EDITORIALS

Silencing Immune Dialogue in Multiple Sclerosis

Stephen L. Hauser, M.D.

Multiple sclerosis has two principal forms. Relapsing multiple sclerosis is characterized by recurrent attacks, initially with remissions but over time leading to lasting disability. In progressive multiple sclerosis, continuous worsening that leads to a wheelchair- or bed-bound state is typical. Progressive multiple sclerosis usually develops after a period of relapsing disease or, less commonly, is present from onset. Relapsing multiple sclerosis is primarily a disorder of the adaptive immune system (B and T lymphocytes) that is orchestrated by circulating B lymphocytes that traffic into the central nervous system. Progression, by contrast, is mediated by both the adaptive and innate immune systems — B and T cells, as well as resident microglia and macrophages — that are located behind an intact blood–brain barrier, impermeable to most systemically administered drugs.

In this issue of the *Journal*, Vermersch and colleagues[1] report the results of a phase 2 trial involving patients with relapsing multiple sclerosis in which the investigators tested frexalimab, an inhibitor to the CD40 ligand (CD40L), a costimulatory molecule expressed on T lymphocytes that is essential for interactions with antigen-presenting cells. The trial was brief; the primary end point was the number of new areas of gadolinium enhancement, a magnetic resonance imaging (MRI) marker for focal breakdown of the blood–brain barrier, developing between 8 weeks and 12 weeks after the start of treatment. Gadolinium leakage into the brain is a surrogate for focal inflammation and clinical relapses.

What can we conclude from these preliminary data? The results appear clear, although the clinical significance is uncertain — clear because there was an unambiguous benefit with regard to short-term MRI outcomes in patients who received frexalimab as compared with those who received placebo and because a generally low level of MRI activity persisted during an additional 12-week open-label extension period. A similar decrease in MRI activity was also observed in patients in the placebo group who crossed over to receive frexalimab therapy in the extension period. Positive results with frexalimab were supported by the lower levels of neurofilament light chains in peripheral blood, a biomarker of brain-tissue damage. If these benefits are confirmed with longer-term use of the agent, it seems likely that there will be a protective effect of frexalimab therapy with regard to relapses of multiple sclerosis. Nevertheless, some questions have not yet been addressed.

Because of its role as a key costimulatory molecule that mediates interactions between T lymphocytes and B cells as well as other antigen-presenting cells, blockade of CD40–CD40L engagement is a rational therapeutic strategy in multiple sclerosis. This approach has genetic support. An intronic single-nucleotide polymorphism within CD40 modestly increases the risk of multiple sclerosis. This variant has contrasting functional effects on the biologic characteristics of B cells, increasing expression of the CD40 protein, acting as a splice variant altering the production of secreted CD40 isoforms that can be stimulatory or inhibitory, and decreasing the levels of the regulatory cytokine interleukin-10.[2] The last of these potentially promotes deleterious proinflammatory polarization of B cells that are characteristic of multiple sclerosis.[3] One earlier

trial of an inhibitor of a different costimulatory molecule (CTLA4) showed no effect on relapsing multiple sclerosis,[4] and the blocking of B-cell activity with atacicept, a decoy receptor for the B-cell survivor factors APRIL (a proliferation-inducing ligand) and B-lymphocyte stimulator (BLyS), paradoxically worsened multiple sclerosis.[5] Thus, the complexities of immunoregulatory networks in multiple sclerosis require cautious translation to the bedside.

The depletion of circulating B cells with the use of anti-CD20 monoclonal antibodies[6,7] has become a mainstay of treatment in multiple sclerosis. Their rapid onset of effect has indicated that B-cell antigen presentation[8] and cytokine secretion,[3] rather than antibody production, are likely to be responsible for their benefit — a situation that emphasizes the central role of B-cell antigen presentation to T cells and the effects on B-cell cytokines as mediators of tissue damage. Highly effective therapies against relapsing multiple sclerosis, with the anti-CD20 agents or the $\alpha 4\beta 1$ integrin inhibitor natalizumab,[9] have shown that when relapses are prevented, a progression independent of disease activity is uncovered; this progression was previously obscured by fluctuating neurologic findings that were due to relapses and partial remissions. Thus, progression is present in most, if not all, patients with multiple sclerosis, regardless of where they are in the disease continuum. In addition to marked effects against relapses, B-cell–based therapies provide partial benefits against progression,[10] a finding that suggests that removal of B cells may also reduce microglial activation and neurodegeneration, components of the pathologic features of progressive multiple sclerosis.

The striking clinical benefits and safety profile of the available high-efficacy therapies for relapsing multiple sclerosis create a high bar for any new treatment. In this trial, the MRI outcomes with frexalimab therapy were impressive but appear to be less complete than those with anti-CD20 agents, although trials of different agents cannot be directly compared. Safety with long-term use is another unknown. Even if future studies show frexalimab to be competitive with currently available therapies for relapsing multiple sclerosis, the paramount need is for more effective therapy against progression.

Inhibitors of the CD40 pathway could downregulate innate immunity in the central nervous system, a major contributor to progressive multiple sclerosis. The blockade of CD40L signaling on microglia at plaque edges, in normal-appearing white matter, and on meningeal macrophages may neutralize their proinflammatory tissue-damaging properties, if adequate drug concentrations in tissue are reached. MRI surrogates for microglial injury and pathologic features of progressive multiple sclerosis — slowly evolving and paramagnetic rim lesions — were evaluated as exploratory end points in this trial, but data on these end points are not reported; these results are awaited with interest. Although the current trial was neither designed nor powered to assess benefits against progressive multiple sclerosis, progression is where the true clinical value of frexalimab, and its place in the therapeutic armamentarium against multiple sclerosis, will need to be defined.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the UCSF Weill Institute for Neurosciences and the Department of Neurology, University of California, San Francisco, San Francisco.

1. Vermersch P, Granziera C, Mao-Draayer Y, et al. Inhibition of CD40L with frexalimab in multiple sclerosis. N Engl J Med 2024;390:589-600.
2. Smets I, Fiddes B, Garcia-Perez JE, et al. Multiple sclerosis risk variants alter expression of co-stimulatory genes in B cells. Brain 2018;141:786-96.
3. Li R, Rezk A, Miyazaki Y, et al. Proinflammatory GM-CSF–producing B cells in multiple sclerosis and B cell depletion therapy. Sci Transl Med 2015;7(310):310ra166.
4. Khoury SJ, Rochon J, Ding L, et al. ACCLAIM: a randomized trial of abatacept (CTLA4-Ig) for relapsing-remitting multiple sclerosis. Mult Scler 2017;23:686-95.
5. Kappos L, Hartung HP, Freedman MS, et al. Atacicept in multiple sclerosis (ATAMS): a randomised, placebo-controlled, double-blind, phase 2 trial. Lancet Neurol 2014;13:353-63.
6. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon Beta-1a in relapsing multiple sclerosis. N Engl J Med 2017;376:221-34.
7. Hauser SL, Bar-Or A, Cohen JA, et al. Ofatumumab versus teriflunomide in multiple sclerosis. N Engl J Med 2020;383:546-57.
8. Wang J, Jelcic I, Mühlenbruch L, et al. HLA-DR15 molecules jointly shape an autoreactive T cell repertoire in multiple sclerosis. Cell 2020;183(5):1264-1281.e20.
9. Kappos L, Butzkueven H, Wiendl H, et al. Greater sensitivity to multiple sclerosis disability worsening and progression events using a roving versus a fixed reference value in a prospective cohort study. Mult Scler 2018;24:963-73.
10. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med 2017;376:209-20.

DOI: 10.1056/NEJMe2314434